Asian Journal of Chemistry; Vol. 26, No. 8 (2014), 2437-2442

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16244

Asymmetric Synthesis, Characterization and Stereoselectivity of Novel 1-{2-[(1R,2S)-2-(Chloromethyl)cyclopropyl]ethyl}-4-methoxybenzene *via* Boronate Complex

HABIB HUSSAIN*, SYEDA RUBINA GILANI, ZULFIQAR ALI and IMDAD HUSSAIN

Department of Chemistry, University of Engineering and Technology, Lahore, Pakistan

*Corresponding author: Tel: +92 321 4618681; E-mail: hbubak@gmail.com

Received: 26 August 2013; *Accepted*: 23 September 2013; *Published online*: 15 April 2014; AJC-15044

Novel 1-[2-{(1R,2S)-2-(chloromethyl)cyclopropyl]ethyl}-4-methoxybenzene was synthesized by cyclopropanation reaction through a novel route. Carbamate was reacted with 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to form boronic ester which was further treated with 1-bromo-3,5-*bis*(trifluoromethyl)benzene in the presence of *n*-BuLi and nucleophilic boronate complex was synthesized. 1-[2-{(1R,2S)-2-(chloromethyl)cyclopropyl]ethyl}-4-methoxybenzene was then prepared by reacting boronate complex with different electrophiles like trichloroisocyanuric acid (TCCA) and N-chlorosuccinimide (NCS). Yields and diastereomeric ratios (d.r) were studied by using various aryl lithiums and electrophiles at different temperatures. Best yield, diastereomeric ratio (d.r), enantiomeric ratio (e.r), enantiomeric excess (e.e), enantiospecificity and $[\alpha]_D$ were 67 %, 2.1:1, 68.6:28.9, 39.7, 0.41 and +3.84, respectively.

Keywords: Boronic ester, Boronate complex, Aryllithium, Electrophiles, Cyclopropanation, Stereoselectivity.

INTRODUCTION

In the past decade, there has been great interest in the development of catalytic enantioselective methods for the preparation of chiral, optically enriched organoboronates as precursors of enantio-enriched compounds. There is a wide use of organometallic nucleophiles in organic synthesis but there are a few chiral examples of these useful reagents. Organic synthesis usually involves combination of many nucleophiles with electrophiles. Boronate complexes containing stereogenic boron act as nucleophiles[1] and were synthesized by reacting trivalent borons with different nucleophiles[2,3]. Kaiser *et al.*[4] prepared boronate complex (99 % e.e) without racemization at boron through chirality transfer from a carbon. Chang *et al.*[5] synthesized chiral alkylboronates in high yields and 98 % e.e by reacting Grignard reagent with unsaturated esters and thioesters. Gauthier *et al.*[1] converted boronic esters into reactive nucleophiles and resulting boronate complexes were reacted with a number of electrophiles with inversion of stereochemistry. Lou *et al.*[6], Chong *et al.*[7] and Goodman and Pellegrinet[8] synthesized reactive boronate species by replacing alkoxy groups with biphenols. Vedejs *et al.*[9] converted many amino acids into asymmetric boronate complexes. Boronate complexes had been used as reaction intermediates for the synthesis of many useful asymmetric products. Lessard *et al.*[10] reacted chiral allylic boronate to various aldehydes and synthesized useful α-hydroxyalkyl derivatives in high stereoselectivity. Hall *et al.*[11] prepared many alcohols and amines from alkyl boronates in good yields.

In recent study, we developed a novel route for the synthesis of novel 1-[2-{(1R,2S)-2-(chloromethyl)cyclopropyl]-ethyl}-4-methoxybenzene (**9**) by using boronate complexes as nucleophiles. Boronic esters were converted into reactive nucleophilic boronate complexes by reacting with some aryl litium and after combining with certain electrophiles desired product was obtained. Reaction was investigated at different temperatures using various aryllithiums and electrophiles to get the best yields and stereoselectvity. High yields and d.r were obtained by tuning the temperature with different aryl lithium and electrophiles like trichloroisocyanuric acid (TCCA) and N-chlorosuccinimide (NCS).

EXPERIMENTAL

N,N-Diisopropylcarbamoyl chloride, 3-(4-methoxyphenyl)-1-propanol, *n*-butyl lithium (*n*-BuLi), *sec*-butyl lithium solution (*s*-BuLi) (1.6 M), allylboronic acid pinacol ester, (-) sparteine, N,N,N,N-tetramethyl-ethylenediamine (TMEDA), 1,3-*bis*(trifluoromethyl)-5-bromobenzene, 1-bromonaphthalene, N-chlorosuccinimide (NCS) and trichloroisocyanuric acid (TCCA) were purchased form Sigma Aldrich while triethylamine was purchased from Fischer. All chemicals were used as such as received. Anhydrous dichloromethane (DCM), diethyl ether, acetonitrile and tetrahydrofuran (THF) were obtained after distillation with sodium benzophenone

ketyl under nitrogen and stored in Young's flasks over 4 Å molecular sieves. N,N,N,N-tetramethylethylene-diamine (TMEDA) was distilled over CaH_2. Being air and water sensitive, all reactions were carried out in flame-dried glass-ware under nitrogen atmosphere using standard Schlenk lines.

Synthesis of 3-(4-methoxyphenyl)propyl-N,N-diisopropylcarbamate (4): Triethylamine (Et_3N) (5 mL, 36.1 mmol, 1.2 eq) (**3**) was added to a solution of N,N-diisopropylcarbamoyl chloride (5.43 g, 33.1 mmol, 1.1 eq.) (**1**) and 3-(4-methoxyphenyl)-1-propanol (5 g, 30.1 mmol, 1.0 eq.) (**2**) in CH_2Cl_2 (30 mL) at room temperature. The resulting mixture was refluxed for 16 h, allowed to cool to room temperature and quenched with 1 N NaOH (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl, water and brine, dried ($MgSO_4$), concentrated and purified by column chromatography (SiO_2, 90:10 petrol/EtOAc) to obtain the desired 3-(4-methoxyphenyl)propyl-N,N-diisopropylcarbamate (**4**) (8.69 g, 99 %) as white solid (Fig. 1.)

Carbamate (**4**) was characterized through ^{1}H NMR, ^{13}C NMR and functional groups were confirmed through IR. This crude product (**4**) was used for the synthesis of (R)-2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6**) and 2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**7**).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.10 (2H, d, J = 8.80 Hz, 2 × Ar*H*) 6.83 (2H, d, J = 8.80 Hz, 2 × Ar*H*) 4.10 (2H, t, J = 6.5 Hz, OCH_2) 3.96 (2H, br s, 2 × -C*H*$(CH_3)_2$) 3.78 (3H, s, OCH_3) 2.62-2.69 (2H, m, CH_2CH_2CH_2O) 1.90-1.98 (2H, m, CH$_2$CH_2CH$_2$O) 1.22 (12H, d, J = 6.85 Hz, 4 × CH_3) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.8 (1C, N*C*OO), 155.8 (1C, Ar*C*), 133.6 (1C, Ar*C*), 129.3 (2C, 2 × Ar*C*H), 113.8 (2C, 2 × Ar*C*H), 64.0 (1C, CH$_2$CH$_2$*C*H$_2$O), 55.2 (1C,O*C*H$_3$), 45.8 (2C, br, 2 × *C*H$(CH_3)_2$), 31.6 (1C,*C*H$_2$CH$_2$CH$_2$O), 31.1 (1C,CH$_2$*C*H$_2$CH$_2$O), 21.0 (4C, br, 4 × *C*H$_3$). IR (film): ν(cm^{-1}) 3026 (sp^2 C-H Stretch), 2967, 2868 (sp^3 C-H stretch), 1685 (C=O stretch), 1512, 1435 (*sp*^{2} C=C stretch), 1288, 1244 (*sp*^{3} C-O stretch), 832, 771 (*sp*^{2} C-H oop bending). m.p = 36-38 °C

Synthesis of (R)-2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6): To a solution of primary carbamate (2 g, 6.82 mmol, 1.0 eq) (**4**) and (-) sparteine (1.88 mL, 8.18 mmol, 1.2 eq.) (**5a**) in Et_2O (34 mL) at -78 °C was added *sec*-BuLi (1.6 M in 92:8 cyclohexane/hexane, 5.8 mL, 7.50 mmol, 1.1 eq.) dropwise. The resulting mixture was stirred for 5 h at -78 °C before allylboronic acid pinacol ester (1.53 mL, 8.18 mmol, 1.2 eq.) (**5**) was dropwise added. The reaction mixture was further stirred at -78 °C for 1 h, allowed to warm to room temperature. A solution of $MgBr_2$·OEt_2 in Et_2O, made as follows, was added to the reaction mixture at this point: [1,2-dibromoethane (1.19 mL, 13.77 mmol, 1.0 eq) was added to a suspension of magnesium (0.33 g, 13.77 mmol, 1.0 eq.) in Et_2O (17.2 mL) at room temperature. The reaction flask was then placed into a water bath in order to control the moderate exotherm and was further stirred for 2 h. Both layers of the biphasic mixture thus obtained were transferred to the former mixture *via* syringe. The mixture was refluxed for 16 h.

The reaction mixture was allowed to cool down to room temperature and was carefully quenched with water. Diethyl ether was added, the layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with 1N HCl, 1N NaOH, water and brine, dried $MgSO_4$, concentrated and purified by column chromatography (SiO_2) to obtain the pure (R)-2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6**) (1.67 g, 77.6 %) as colorless oil (Fig. 2).

Complete characterization was done by ^{1}H NMR, ^{13}C NMR and IR. Fine peaks confirmed the purity of the secondary boronic ester (**6**) and it was used as starting material for reaction (Fig. 4). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.09 (2H, d, J = 8.80 Hz, 2 × Ar*H*) 6.81 (2H, d, J = 8.80 Hz, 2 × Ar*H*) 5.86-5.75 (1H, m, C*H*=CH$_2$) 5.04 (1H, d, J = 2.20 Hz, CH=CH*H*) 4.94 (1H, d, J = 10.27 Hz, CH=C*H*H) 3.78 (3H, s, OCH_3) 2.63-2.48 (2H, m, ArCH_2CH$_2$CHBCH$_2$) 2.27-2.11 (2H, m, ArCH$_2$CH$_2$CHBCH_2) 1.78-1.58 (2H, m, ArCH$_2$CH_2CHB CH$_2$) 1.25 (12H, s, 4 × CH_3) 1.08-1.18 (1H, m, ArCH$_2$CH$_2$C*H*B CH$_2$) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.6 (1C, -O*C*H$_3$), 138.4 (2C, 2 × Ar*C*H), 135.0 (2C, 2 × Ar*C*H), 129.2 (1C, Ar*C*-O), 114.9 (1C, -CH$_2$*C*H=CH$_2$), 113.6 (1C, -CH=*C*H$_2$), 83.0 (2C, 2 × *C*$(CH_3)_2$), 55.2 (1C, Ar*C*CH$_2$), 35.3 (1C, -*C*H$_2$CH$_2$CHB), 34.5 (1C, -CH$_2$*C*HB), 33.1 (1C, -CHB*C*H$_2$CH), 24.9 (1C, -CH$_2$*C*H$_2$CHB), 24.8 (4C, 2 × $(CH_3)_2$C).^{11}B NMR (96.23 MHz, None) δ ppm 33.24. IR (film): ν(cm^{-1}) 3026 (*sp*^{2} C-H Stretch),

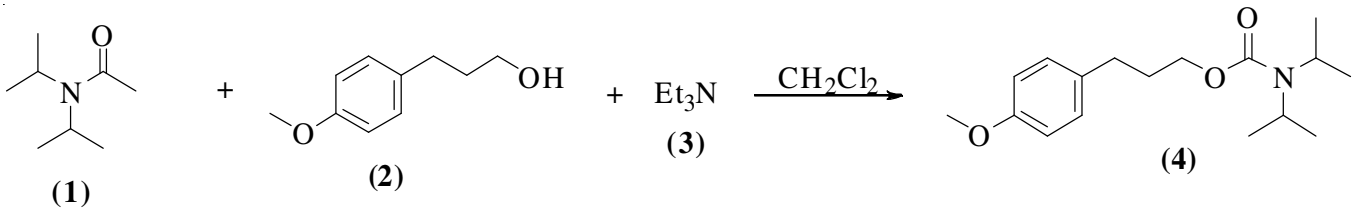


Fig. 1. 3-(4-Methoxyphenyl propyl-N,N-disopropylcarbamate

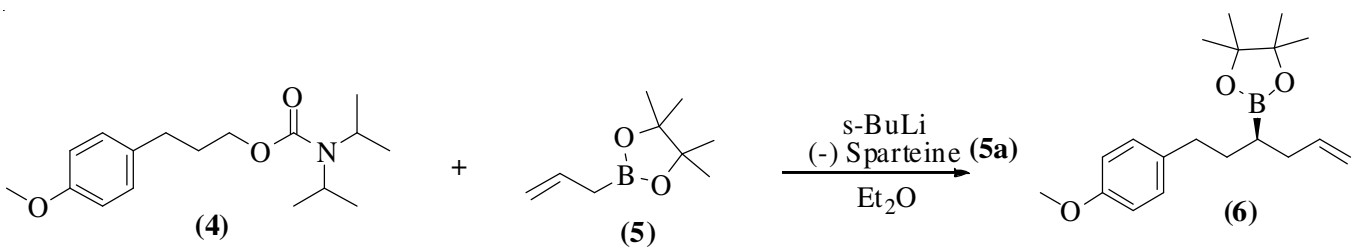


Fig. 2. Synthesis of (R)-2-(1-(4-methoxyphenyl)hex-5-ene-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

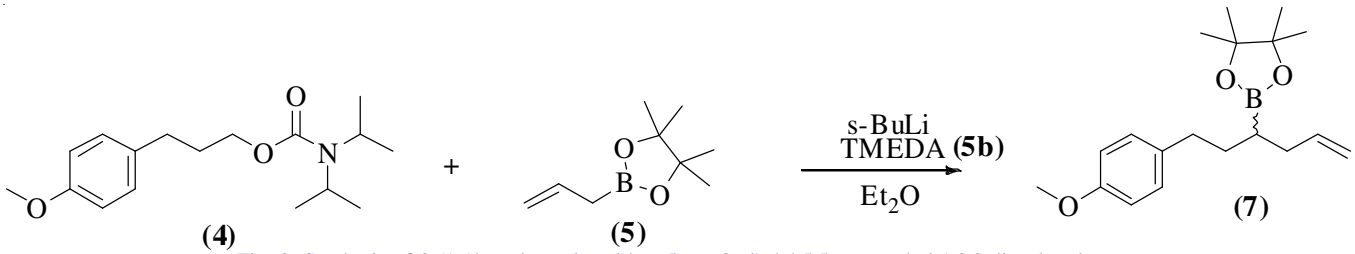
2977, 2924, 2852 (sp^3 C-H stretch), 1511, 1456 (sp^2 C=C stretch), 1243, 1175, 1142 (sp^3 C-O stretch), 846, 822, 670 (sp^2 C-H oop bending).

Synthesis of 2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7): Racemic 2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**7**) was prepared by substituting (-)sparteine by N,N,N,N-tetramethylethylenediamine (TMEDA) (1.22 mL, 8.18 mmol, 1.2 eq.) (**5b**) (Fig. 3).

Pure *sec*-boronic ester (**7**) was collected as colorless oil (1.62g, 75.3 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.09 (2H, d, *J* = 8.80 Hz, 2 × Ar*H*) 6.81 (2H, d, *J* = 8.80 Hz, 2 × Ar*H*) 5.86-5.75 (1H, m, C*H*=CH_2) 5.04 (1H, d, *J* = 2.20 Hz, CH=CH*H*) 4.94 (1H, d, *J* = 10.27 Hz, CH=C*H*H) 3.78 (3H, s, OCH_3) 2.63-2.48 (2H, m, ArCH_2CH_2CHBCH_2) 2.27-2.11 (2H, m, ArCH_2CH_2CHBCH_2) 1.78-1.58 (2H, m, ArCH_2CH_2CHB-CH_2) 1.25 (12H, s, 4 × CH_3) 1.08-1.18 (1H, m, ArCH_2CH_2CH-BCH_2) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.6 (1C, -OCH_3), 138.4 (2C, 2 × Ar*C*H), 135.0 (2C, 2 × Ar*C*H), 129.2 (1C, Ar*C*-O), 114.9 (1C, -CH_2*C*H=CH_2), 113.6 (1C, -CH=*C*H_2), 83.0 (2C, 2 × *C*(CH_3)2), 55.2 (1C, Ar*C*CH_2), 35.3 (1C, -*C*H_2CH_2-CHB), 34.5 (1C, -CH_2*C*HB), 33.1 (1C, -CHB*C*H_2CH), 24.9 (1C, -CH_2*C*H_2CHB), 24.8 (4C, 2 × $(CH_3)_2$C). ^{11}B NMR (96.23 MHz, None) δ ppm 33.24. IR (film): ν(cm^{-1}) 3390 (O-H stretch), 3001 (sp^2 C-H stretch), 2931, 2835 (sp^3 C-H stretch), 1511, 1441 (sp^2 C=C stretch), 1244, 1177, 1036 (sp^3 C-O stretch), 915, 822 (sp^2 C-H oop bending).

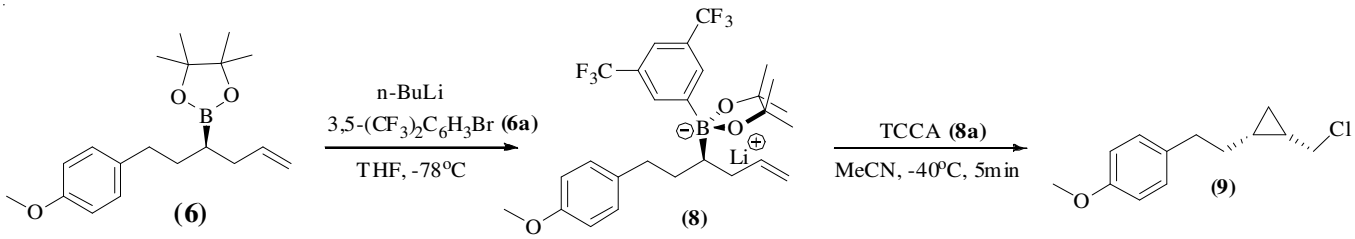
Synthesis of 1-(2-((1R,2S)-2-(chloromethyl)cyclopropyl)-ethyl)-4-methoxybenzene (9): To a solution of 1,3-*bis*(trifluoromethyl)-5-bromobenzene (0.08 g, 0.274 mmol, 1.2 eq) (**6a**) in THF (2.4 mL) at -78 °C was added *n*-BuLi (1.6 M in hexane, 0.17 mL, 0.274 mmol, 1.2 eq.) dropwise. The mixture was stirred 1 h at -78 °C before a solution of boronic ester (0.072 g, 0.228 mmol, 1.0 eq.) (**6**) in THF (1.2 mL) was added dropwise. The reaction mixture was stirred for 0.5 h at -78 °C and 0.5 h at room temperature to give the boronate complex solution (**8**). The reaction mixture was cooled to -40 °C, a solution of TCCA (0.064 g, 0.274 mmol, 1.2 eq.) (**8a**) in MeCN (1.2 mL) was then added dropwise over 1min and the reaction mixture was stirred for 5 min at -40 °C. 20 % $Na_2S_2O_3$ (3 mL) was added at -40 °C and the reaction mixture was allowed to warm to room temperature (Fig. 4). EtOAc was dded and the layers were separated. The aqueous phase was extracted with EtOAc, the organic layers were combined, washed with brine, dried ($MgSO_4$), concentrated. The crude mixture was finally purified by column chromatography (SiO_2, 99:1 Pentane/EtOAc) to give desired 1-(2-((1R,2S)-2-(chloromethyl)cyclopropyl)-ethyl)-4-methoxybenzene (**9**) as colorless oil (0.025 g, 49 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.12 (2H, d, *J* = 8.31 Hz, 2 × Ar*H*) 6.83 (2H, d, *J* = 8.80 Hz, 2 × Ar*H*) 3.79 (3H, s, OCH_3) 3.69 (0.7H, dd, *J* = 11.25, 7.09 Hz, major C*H*HCl) 3.49-3.34 (0.3 H, minor C*H*HCl, 1H, m, CH*H*Cl) 2.71 (1H, t, *J* = 7.83 Hz, ArC*H*HCH_2CH) 2.66 (1H, t, *J* = 7.70 Hz, ArCH*H*CH_2CH) 1.81-1.71 (0.7 H, m, major ArCH_2C*H*HCH) 1.65-1.43 (0.3H, minor ArCH_2C*H*HCH, 1H, m, ArCH_2CH-*H*CH) 1.33-1.22 (0.7H, m, major CH(CH_2)C*H*CH_2Cl) 1.06-0.95 (0.3H, minor CH(CH_2)C*H*CH_2Cl, 0.7H, m, C*H*(CH_2)CH-CH_2Cl) 0.88-0.81 (0.3H, m, CH(C*H*H)CHCH_2Cl) 0.79-0.70 (0.3H, m, C*H*(CH_2)CHCH_2Cl) 0.54-0.46 (1H, m, CH(CH*H*)-CHCH_2Cl) 0.06 (0.7H, q, *J* = 5.54 Hz, CH(CH*H*)CHCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.77 (1C, major, Ar*C*), 157.71 (1C, minor, Ar*C*), 134.25 (1C, major, Ar*C*), 134.21 (1C, minor, Ar*C*), 129.32 (1C, major, Ar*C*), 113.72 (1C, minor, Ar*C*), 113.69 (1C, major, Ar*C*), 55.26 (1C, major, OCH_3), 55.24 (1C, minor, OCH_3), 50.22 (1C, minor, *C*H_2Cl), 46.65 (1C, major, *C*H_2Cl), 35.63 (1C, minor, CH_2*C*H_2CH(CH_2)CH-CH_2Cl), 35.26 (1C, major, *C*H_2CH_2CH(CH_2)CHCH_2Cl), 34.69 (1C, minor, *C*H_2CH_2CH(CH_2)CHCH_2Cl), 30.54 (1C, major, CH_2*C*H_2CH(CH_2)CHCH_2Cl), 21.34 (1C, minor, CH_2CH_2CH-(CH_2)*C*HCH_2Cl), 19.83 (1C, minor, CH_2CH_2*C*H(CH_2)CH-CH_2Cl), 18.54 (1C, major, CH_2CH_2CH(CH_2)*C*HCH_2Cl), 17.72 (1C, major, CH_2CH_2*C*H(CH_2)CHCH_2Cl), 12.93 (1C, minor, CH_2CH_2CH(*C*H_2)CHCH_2Cl), 12.11 (1C, major, CH_2CH_2CH (*C*H_2)CHCH_2Cl). IR (film): ν (cm^{-1}) 3026 (sp^2 C-H stretch), 2977, 2930, 2855, 2835 (sp^3 C-H stretch), 1510, 1455 (sp^2 C=C stretch), 1242, 1176, 1035 (sp^3 C-O stretch), 822, 696, 575 (sp^3 C-Cl stretch). HRMS (ESI) calcd. for $C_{13}H_{17}OCl$ $[M+H]^+$ 225.1039, found 225.1039. $[\alpha]_D$ +3.84 (c 0.52, $CDCl_3$)

SFC separation conditions: Chiralpak IA column with guard, 5 % *i*PrOH in hexane, flow rate: 2 mL/min, 39.9 °C; *t*R



(4) (5) (7)

Fig. 3. Synthesis of 2-(1-(4-methoxyphenyl)hex-5-ene-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



(6) (8) (9)

Fig. 4. Synthesis of 1-(2-((1R,2S)-2(chloromethyl)cyclopropyl)ethyl)-4-methoxybenzene

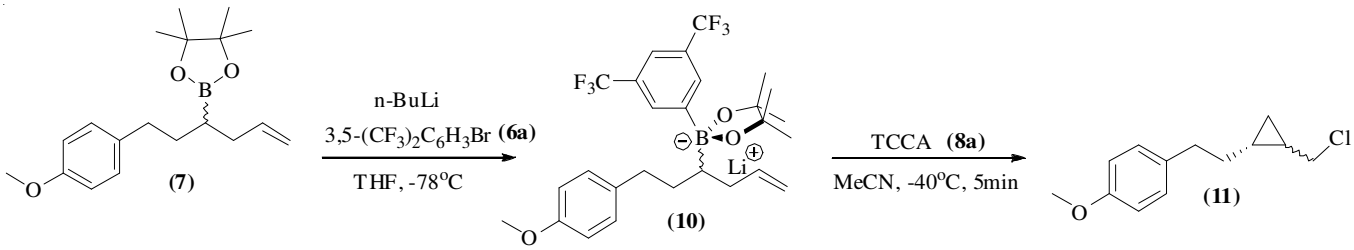


Fig. 5. Synthesis of 1-(2-((1R)-2(chloromethyl)cyclopropyl)ethyl)-4-methoxybenzene

16.5 min for (R)-enantiomer (minor) and *t*R 23.0 min for (*S*)-enantiomer (major). e.r. = 68.6:28.9.

Synthesis of 1-(2-((1R)-2-(chloromethyl)cyclopropyl)-ethyl)-4-methoxybenzene (11): Product 1-(2-((1R)-2-(chloromethyl)cycloprpyl)ethyl)-4-methoxybenzene (**11**) was synthesized by substituting starting material (**6**) with racemic boronic ester (**7**) (Fig. 5).

Pure product (**11**) was obtained as colorless oil (0.024, 48.6 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.12 (2H, d, *J* = 8.31 Hz, 2 × Ar*H*) 6.83 (2H, d, *J* = 8.80 Hz, 2 × Ar*H*) 3.79 (3H, s, OC*H*$_3$) 3.69 (0.7H, dd, *J* = 11.25, 7.09 Hz, major C*H*HCl) 3.49-3.34 (0.3H, minor C*H*HCl, 1H, m, CH*H*Cl) 2.71 (1H, t, *J* = 7.83 Hz, ArC*H*HCH$_2$CH) 2.66 (1H, t, *J* = 7.70 Hz, ArCH*H*CH$_2$CH) 1.81-1.71 (0.7H, m, major ArCH$_2$C*H*HCH) 1.65-1.43 (0.3H, minor ArCH$_2$C*H*HCH, 1H, m, ArCH$_2$CH-*H*CH) 1.33-1.22 (0.7H, m, major CH(CH$_2$)C*H*CH$_2$Cl) 1.06-0.95 (0.3H, minor CH(CH$_2$)C*H*CH2Cl, 0.7H, m, C*H*(CH$_2$)CH-CH$_2$Cl) 0.88-0.81 (0.3H, m, CH(C*H*H)CHCH$_2$Cl) 0.79-0.70 (0.3H, m, C*H*(CH$_2$)CHCH$_2$Cl) 0.54-0.46 (1H, m, CH(CH*H*)-CHCH$_2$Cl) 0.06 (0.7H, q, *J* = 5.54 Hz, CH(C*H*H)CHCH$_2$Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.77 (1C, major, Ar*C*), 157.71 (1C, minor, Ar*C*), 134.25 (1C, major, Ar*C*), 134.21 (1C, minor, Ar*C*), 129.32 (1C, major, Ar*C*), 113.72 (1C, minor, Ar*C*), 113.69 (1C, major, Ar*C*), 55.26 (1C, major, O*C*H$_3$), 55.24 (1C, minor, O*C*H$_3$), 50.22 (1C, minor, *C*H$_2$Cl), 46.65 (1C, major, *C*H$_2$Cl), 35.63 (1C, minor, CH$_2$*C*H$_2$CH(CH$_2$)CHCH$_2$Cl), 35.26 (1C, major, *C*H$_2$CH$_2$CH(CH$_2$)CHCH$_2$Cl), 34.69 (1C, minor, *C*H$_2$CH$_2$CH(CH$_2$)CHCH$_2$Cl), 30.54 (1C, major, CH$_2$*C*H$_2$CH(CH$_2$)CHCH$_2$Cl), 21.34 (1C, minor, CH$_2$CH$_2$-CH(CH$_2$)*C*HCH$_2$Cl), 19.83 (1C, minor, CH$_2$CH$_2$*C*H(CH$_2$)CH-CH$_2$Cl), 18.54 (1C, major, CH$_2$CH$_2$CH(CH$_2$)*C*HCH$_2$Cl), 17.72 (1C, major, CH$_2$CH$_2$*C*H(CH$_2$)CHCH$_2$Cl), 12.93 (1C, minor, CH$_2$CH$_2$CH(*C*H$_2$)CHCH$_2$Cl), 12.11 (1C, major, CH$_2$CH$_2$CH-(*C*H$_2$)CHCH$_2$Cl). IR (film): ν(cm^{-1}) 3026 (*sp*^{2} C-H stretch), 2977, 2930, 2855, 2835 (*sp*^{3} C-H stretch), 1510, 1455 (*sp*^{2} C=C stretch), 1242, 1176, 1035 (*sp*^{3} C-O stretch), 822, 696, 575 (*sp*^{3} C-Cl stretch). HRMS (ESI) calcd. for $C_{13}H_{17}OCl$ [M+H]$^+$ 225.1039, found 225.1039.

SFC separation conditions: Chiralpak IA column with guard, 5% *i*PrOH in hexane, flow rate: 2 mL/min, 39.9 °C; *t*R 16.5 min for (R)-enantiomer (minor) and *t*R 23.0 min for (S)-enantiomer (major).

Synthesis of (R)-1-(4-methoxyphenyl)hex-5-en-3-ol (12)

Oxidation of (R)-2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6): A solution of 3M NaOH/30 % H_2O_2 (2:1 v/v, 1 mL) was added dropwise to a solution of ((R)-2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6**) (0.03 g, 0.115 mmol) in THF/Et_2O (1:1 v/v, 1mL) at 0 °C under vigorous stirring. The reaction mixture was allowed to warm to room temperature and further stirred for 2 h. Et_2O and water was added and phases were separated. The aqueous phase was extracted with Et_2O; the combined organic layers were washed with brine, dried ($MgSO_4$), concentrated and purified by column chromatography (SiO_2) to obtain the pure (R)-1-(4-methoxyphenyl)hex-5-en-3-ol (**12**) as colourless oil (0.022 g, 73.3 %) (Fig. 6).

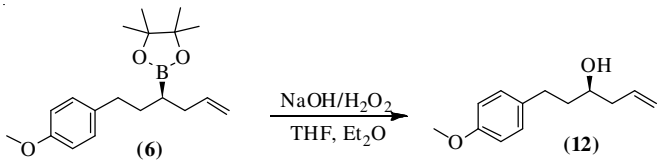


Fig. 6. Synthesis of (R)-1-(4-methoxyphenyl)hex-5-en-3-ol

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.12 (2H, d, *J* = 8.80 Hz, 2 × Ar*H*) 6.83 (2H, d, *J* = 8.56 Hz, 2 × Ar*H*) 5.82 (1H, dddd, *J* = 17.64, 9.63, 7.95, 6.60 Hz, C*H*=CH$_2$) 5.17-5.14 (1H, m, CH=CH*H*) 5.14-5.11 (1H, m, CH=C*H*H) 3.79 (3H, s, OC*H*$_3$) 3.66 (1H, br s, -O*H*) 2.80-2.70 (1H, m, ArC*H*HCH$_2$CHBCH$_2$) 2.68-2.59 (1H, m, ArCH*H*CH$_2$CHB-CH$_2$) 2.36-2.27 (1H, m, ArCH$_2$CH$_2$CHBC*H*H) 2.23-2.12 (1H, m, ArCH$_2$CH$_2$CHBCH*H*) 1.79-1.72 (2H, m, ArCH$_2$C*H*$_2$CH-BCH$_2$) 1.60 (1H, br s, ArCH$_2$CH$_2$C*H*BCH$_2$) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.7 (1C, -O*C*H$_3$), 134.6 (2C, 2 × Ar*C*H), 134.0 (2C, 2 × Ar*C*H), 129.2 (1C, Ar*C*-O), 118.2 (1C, -CH$_2$*C*H =CH$_2$), 113.8 (1C, -CH=*C*H$_2$), 69.8 (1C, -CH$_2$*C*HB), 55.2 (1C, Ar*C*CH$_2$), 42.0 (1C, -CHB*C*H$_2$CH, 38.6 (1C, -CH$_2$*C*H$_2$CHB), 31.0 (1C, -CH$_2$*C*H$_2$CHB). IR (film): ν (cm^{-1}) 3026 (*sp*^{2} C-H stretch), 2977, 2924, 2852 (*sp*^{3} C-H stretch), 1511, 1456 (*sp*^{2} C=C stretch), 1243, 1175, 1142 (*sp*^{3} C-O stretch), 846, 822, 670 (*sp*^{2} C-H oop bending).

SFC separation conditions: Chiralpak IA column with guard, 5 % *i*PrOH in hexane, flow rate: 2 mL/min, 39.9 °C; *t*R 11.4 min for (S)-enantiomer (minor) and *t*R 13.2 min for (R)-enantiomer (major). $[\alpha]_D$ 20 + 0.20 (c 1.0, $CHCl_3$), e.r. = 99.0:1.0

The proposed mechanism are shown in Fig. 7.

RESULTS AND DISCUSSION

3-(4-Methoxyphenyl)propyl-N,N-diisopropylcarbamate (**4**) (Table-1, entry 1) was synthesized in excellent yields by reacting N,N-diisopropylacetamide (**1**) and 3-(4-methoxyphenyl)propan-1-ol (**2**) at mentioned conditions. Both chiral (**6**) and racemic (**7**) secondary boronic esters were prepared by lithiation-borylation reaction in good yields. (R)-2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6**) (Table-1, entry 2) was formed by reacting

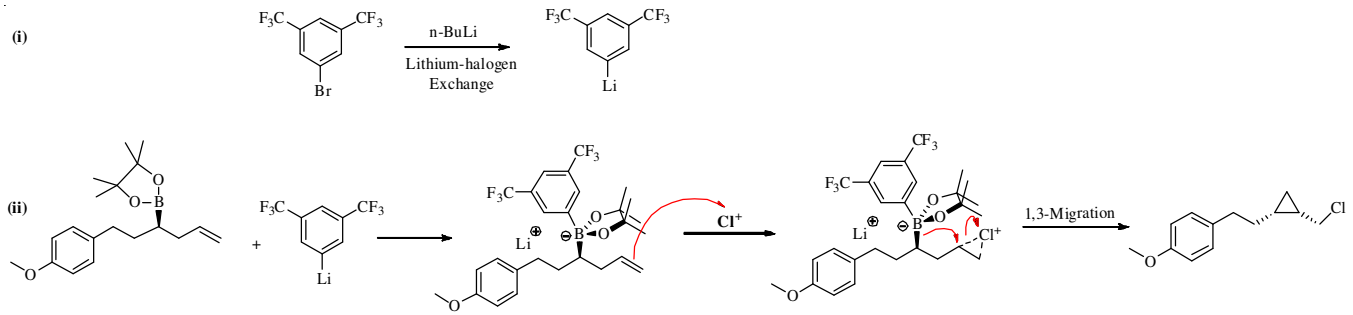


Fig. 7

3-(4-methoxyphenyl)propyl-N,N-diisopropylcarbamate (**4**) with 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5**) in the presence of *sec*-BuLi and (-) sparteine (**5a**) in Et_2O while in the synthesis of 2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**7**) (Table-1, entry 3), TMDA (**5b**) was used instead of (-) sparteine (**5a**). These boronic esters (**6**, **7**) were used in cyclopropanation reaction as starting materials.

Boronate complex (**8**) was then synthesized after reacting (R)-2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6**) with 1,3-*bis*(trifluoromethyl)-5-bromobenzene (**6a**). Boron-ate (**8**) acted as nucleophile and was then combined with some electrophiles like TCCA and NCS, after 1,3-migration it resulted in 1-[2-{(1R,2S)-2-(chloromethyl)cyclopropyl]ethyl}-4-methoxybenzene (**9**). In the same way, boronic ester (**7**) was used to prepare 1-(2-((1R)-2-(chloromethyl)cyclopropyl)ethyl)-4-methoxybenzene (**11**) through boronate complex (**10**). Both chiral and racemic cyclopropanation products (**9, 11**) were synthesized and tuned the reaction for best yields and stereoselectivity.

In order to get best yields and stereoselectivity, reaction (Figs. 4 and 5) was investigated at different temperatures using a number of aryllithiums and electrophiles like TCCA and NCS.

Effect of temperature on the reaction was studied first by reacting boronate complex at different temperatures using TCCA as the electrophilic chlorine source. It was found that at higher temperature (room temperature), both yields and d.r. was worse and favoured the other diastereomer (Table-2, entry 1). So reaction was attempted at lower temperatures -40 °C and -78 °C respectively and found that d.r. was only slightly better. At -40 °C, improvement was seen both in yields and d.r (Table-2, entry 2) so reaction was carried out at further low temperature -78 °C but results were discouraging (Table-2, entry 3).

TABLE-1
PHYSICAL CHARACTERISTIC OF STARTING MATERIALS

Entry	Starting Material	Colour	Yield (%)
1	3-(4-Methoxyphenyl)propyl-N,N-diisopropylcarbamate	White solid	99.0
2	(R)-2-(1-(4-methoxyphenyl) hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane	Colorless oil	77.6
3	2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane	Colorless oil	75.3

TABLE-2
EFFECT OF TEMPERATURE ON STEREOSELECTIVITY

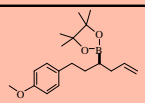
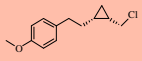
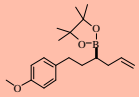
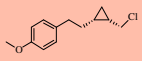
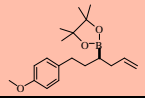
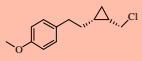
Entry	Boronic Ester	Aryllithium	Electrophile	Temp. (°C)	Product	Yield (%)	d.r (%)
1		3,5-$(CF_3)_2C_6H_3Br$	TCCA	R.T		13	1.18:1
2		3,5-$(CF_3)_2C_6H_3Br$	TCCA	-40		49	2:1
3		3,5-$(CF_3)_2C_6H_3Br$	TCCA	-78		22	2.1:1

TABLE-3
EFFECT OF ARYL LITHIUMS ON STEREOSELECTIVITY

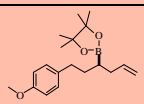
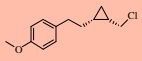
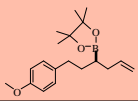
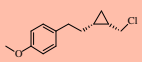
Entry	Boronic Ester	Aryllithium	Electrophile	Temp. (°C)	Product	Yield (%)	d.r (%)
1		3,5-$(CF_3)_2C_6H_3Br$	TCCA	-40		49	2:1
2		1-Bromonaphthalene	TCCA	-40		67	1.8:1

TABLE-4
EFFECT OF ELECTROPHILES ON STEREOSELECTIVITY

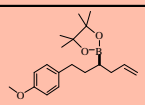
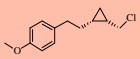
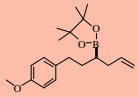
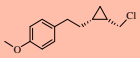
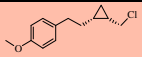
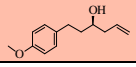
Entry	Boronic Ester	Aryllithium	Electrophile	Temp. (°C)	Product	Yield (%)	d.r (%)
1		3,5-$(CF_3)_2C_6H_3Br$	TCCA	-40		49	12:1
2		3,5-$(CF_3)_2C_6H_3Br$	NCS	-40		18	1.8:1

TABLE-5
DATA SHOWING STEREOSELECTIVITY AND $[\alpha]_D$

Entry	Products	d.r	e.r	e.e	e.s	$[\alpha]_D$
1		2.1:1	68.6:28.9	39.7	0.41	+3.84
2		----	99.0:1.0	98.0	----	+0.20

Then, we investigated if steric bulk of aryl lithium had some affect on stereoselectivity so 3,5-$(CF_3)_2C_6H_3Br$ was replaced by 1-bromonaphthalene at -40 °C. However, the use of 1-bromonaphthalene actually resulted in slightly lower d.r., although yield was slightly improved (Table-3, entry 2).

Similarly, reaction was also tried by changing the electrophiles to see how this would affect the stereoselectivity. In the light of above observations, 3,5-$(CF_3)_2C_6H_3Br$ was used as aryl lithium and temperature was kept -40 °C and reaction was tuned by changing electrophile. Use of NCS instead of TCCA resulted in slightly lower yield and lower diastereoselectivity (Table-4, entry 2).

As analyzed from ^{1}H NMR, cyclopropanation product 1-[2-{(1R,2S)-2-(chloromethyl)cyclopropyl]ethyl}-4-methoxybenzene (**9**) was a mixture of 70:30 (major/minor) diastereomers. For the determination of e.r, (R)-2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6**) was oxidized into (R)-1-(4-methoxyphenyl)hex-5-en-3-ol (0.022g, 73.3 %) (**12**). Enantiomeric ratio determined by supercritical fluid chromatography (SFC) was 68.6:28.9 while enantiomeric excess (e.e), enanatiospecificity (e.s) and $[\alpha]_D$ calculated were 39.7, 0.41 and +3.84, respectively (Table-5, entry 1).

Conclusion

Novel 1-[2-{(1R,2S)-2-(chloromethyl)cyclopropyl]ethyl}-4-methoxybenzene (**9**) was synthesized in good yields (Table-3, entry 2), diastereometric ratios (d.r) and enantiomeric ratios (e.r) (Table-5, entry 1). Temperature had dominant effect on stereoselectivity (Table-2, entry 2). Best yield for this cyclopropanation reaction was 67 % using 1-bromonaphthlene as aryllithium and performing the reaction at -40 °C (Table-3, entry 2). The best diastereoselectivity obtained was 2.1:1, using 1,3-*bis*(trifluoromethyl)-5-bromobenzene at -78 °C (Table-2, entry 3). Enantiomeric ratio (e.r), enantiomeric excess (e.e), enantiospecificity (e.s) and $[\alpha]_D$ for 1-[2-{(1R,2S)-2-(chloromethyl)cyclopropyl]ethyl}-4-methoxybenzene (**9**) were 68.6:28.9, 39.7, 0.41 and +3.84 respectively (Table-5, entry 1).

ACKNOWLEDGEMENTS

The authors are thankful to Higher Education Commission of Pakistan for providing research funds. The authors also acknowledged the Department of Chemistry, University of Engineering and Technology, Lahore, Pakistan and Superior University, Raiwand Road, Lahore, Pakistan for guidance, research and laboratory facilities.

REFERENCES

1. R. Larouche-Gauthier, T.G. Elford and V.K. Aggarwal, *J. Am. Chem. Soc.*, **133**, 16794 (2011).
2. H.C. Brown and A.K. Gupta, *J., Organomet. Chem.*, **341**, 73 (1988).
3. S. Toyota and M. Oki, *Bull. Chem. Soc. Jpn*, **65**, 1832 (1992).
4. P.F. Kaiser, J.M. White and C.A. Hutton, *J. Am. Chem. Soc.*, **130**, 49, 16450 (2008).
5. J.C.H. Lee and D.G. Hall, *J. Am. Chem. Soc.*, **132**, 5544 (2010).
6. S. Lou, P.N. Moquist and S.E. Schaus, *J. Am. Chem. Soc.* **128**, 12660 (2006).
7. D. Chong, A. Nafady, P.J. Costa, M.J. Calhorda and W.E. Geiger, *J. Am. Chem. Soc.*, **127**, 15676 (2005).
8. S.C. Pellegrinet and J.M. Goodman, *J. Am. Chem. Soc.*, **128**, 3116 (2005).
9. E. Vedejs, S.C. Fields, S. Lin and M.R. Schrimpf, *J. Org. Chem.*, **60**, 3028 (1995).
10. S. Lessard, F. Peng and D.G. Hall, *J. Am. Chem. Soc.*, **131**, 9612 (2009).
11. G.D. Hall, J.C.H. Lee and J.Y. Ding, *Pure Appl. Chem.*, **84**, 2263 (2012).